Applied Mathematics Letters 22 (2009) 646–650

Contents lists available at ScienceDirect

Applied Mathematics Letters

journal homepage: www.elsevier.com/locate/aml

On the coupling of higher and lower scales using the mathematical kinetic theory of active particles☆

N. Bellomo*, M. Delitala

Department of Mathematics, Politecnico, Turin, Italy

ARTICLE INFO

Article history:
Received 12 May 2008
Accepted 12 May 2008

Keywords:
Kinetic theory
Active particles
Complexity
Multiscale
Living systems

ABSTRACT

A mathematical framework of the kinetic theory of active particles is derived to couple two interacting systems at different scales. The dynamics at the higher scale is influenced by the lower scale. The analysis is focused on the coupling of multicellular systems in biology to the molecular scale, while the final aim consists in designing mathematical structures to assist towards the derivation of models of complex living systems.

© 2008 Elsevier Ltd. All rights reserved.

1. Introduction

Methods of the mathematical kinetic theory for active particles have been developed, following [1], to model multicellular systems focused on the immune competition as documented in the book [2] and in various recent papers [3,4]. Mathematical models, in the case of space homogeneity, are structured in terms of integro-differential equations that define the evolution of the probability distribution over the microscopic state, called the *activity*, of large systems of interacting entities called *active particles*. The parameters of models can be identified through a phenomenological interpretation of the real system at its specific scale. On the other hand, it is understood that parameters of models at the cellular scale are generated by the dynamics at the molecular (genome) scale [5–8]. The same reasonings can be applied, as documented in [9], to models linking macroscopic and microscopic dynamics.

This present work, following the suggestion of [10] focused on the modelling and mathematical aspects of the early stage of the onset and mutations of cancer cells, deals with the derivation of a general mathematical framework of the kinetic theory for active particles to couple the lower to the higher scale. In detail, Section 2 summarizes the mathematical structures used for the modelling at the cellular scale, Section 3 deals with the derivation of the aforementioned mathematical structures, and finally, the last section proposes a critical analysis from the viewpoint of modelling applications in life sciences.

2. The mathematical framework modelling multicellular systems

Let us consider a system, homogeneously distributed in space, constituted by two interacting cell populations corresponding to cancer and immune cells described, according to the kinetic theory for active particles, by the distribution functions

$$f_i = f_i(t, u) : [0, T] \times D_u \to \mathbb{R}_+ \quad i = 1, 2. \tag{1}$$

☆ Partially supported by RESOLVE, Health-2007-2.2.2-2, Termination of developmental processes and their reactivation in adult life.
* Corresponding author.
E-mail addresses: nicola.bellomo@polito.it (N. Bellomo), marcello.delitala@polito.it (M. Delitala).

0893-9659/$ – see front matter © 2008 Elsevier Ltd. All rights reserved.
doi:10.1016/j.aml.2008.05.005

The mathematical approach and specific models are reported in the book [2], and papers [3,10]. The mathematical framework used for the modelling is as follows:

$$\begin{aligned}\partial_t f_i(t,u) &= J_i[\mathbf{f}](t,u) = C_i[\mathbf{f}](t,u) + P_i[\mathbf{f}](t,u)\\ &= \sum_{j=1}^{2}\int_{D_u}\int_{D_u}\eta_{ij}(u_*,u^*)\mathcal{A}_{ij}(u_*,u^*;u)f_i(t,u_*)f_j(t,u^*)\,\mathrm{d}u_*\,\mathrm{d}u^* - f_i(t,u)\sum_{j=1}^{2}\int_{D_u}\eta_{ij}(u,u^*)f_j(t,u^*)\,\mathrm{d}u^*\\ &\quad+\sum_{h=1}^{2}\sum_{k=1}^{2}\int_{D_u}\int_{D_u}\eta_{hk}(u_*,u^*)\mu_{hk}(i)(u_*,u^*;u)f_h(t,u_*)f_k(t,u^*)\,\mathrm{d}u_*\,\mathrm{d}u^*,\end{aligned}\tag{2}$$

where $i, j, h, k = 1, 2, \ldots$, while, at each time t:

- $C_i[\mathbf{f}](t,u)$ models the flow into the elementary volume of the state space of the ith population due to conservative interactions that modify the state of the interacting pairs without generation of proliferative or destructive events. Moreover, η_{ij} is the rate of encounters between a ***candidate cell***, with state u_* in the ith population, and a ***field particle***, with state u^* in the jth population, while the probability density for, as a result of this interaction, the particle acquiring the state u is denoted by $\mathcal{A}_{ij}(u_*,u^*;u)$.
- $P_i[\mathbf{f}](t,u)$ models the flow into the elementary volume of the state space of the ith population due to proliferation, where $\mu_{hk}(i)(u_*,u^*;u)$ models the net proliferation into the ith population due to interactions which occur with encounter rate η_{hk} between the **candidate particle**, with state u_* of the hth population, and the **field particle**, with state u^* of the kth population. It is worth pointing out that the above term models both interactions with population transition and interactions without population change.

The above mathematical structures can be used, as already mentioned, to derive specific models if the interaction functions that have been defined above are properly identified. A survey and critical analysis on a variety of models that are related to the above frameworks is given in the already cited paper [10]. Of course, dealing with an arbitrary number of populations is simply a matter of additional technical calculations. It is worth stressing that each population is regarded as a module expressing collectively a well defined biological function. This interpretation, discussed in [3], contributes to reducing the complexity of the overall system under consideration according to the theory of modules of Hartwell; see Section 3 of [4].

3. Mathematical structures

Let us now consider the coupling of the system described in the preceding section with the lower scale, where the overall state is defined by the distribution function of gene expression:

$$\varphi = \varphi(t,v) : [0,T]\times D_v \to \mathbb{R}_+,\tag{3}$$

over the microscopic state $v \in D_v$ of the interacting entities regarded as active particles.

The system at the lower scale interacts with the outer environment, that has the ability of modifying the gene expression by an action, known in time, of the type

$$\psi = \psi(t,v) : [0,T]\times D_v \to \mathbb{R}_+,$$

given as a bounded integrable function of time and v

$$\int_0^T\int_{D_v}\psi(t,v)\,\mathrm{d}v\,\mathrm{d}t \le M,\tag{4}$$

for some constant M.

The scheme of interaction from the lower to the higher scale can be represented as follows:

$$[\mathcal{L}\,\varphi = \mathcal{N}[\varphi,\varphi] + \mathcal{M}[\varphi,\psi]] \to [\mathcal{L}\,\mathbf{f} = J[\mathbf{f}] + \mathcal{Q}[\mathbf{f},\varphi]],\tag{5}$$

which corresponds to the dynamics sketched in Fig. 1:

- The evolution of the system at the lower scale is determined by the interaction between active particles within the population, and with particles of the outer environment.
- The evolution of the system at the higher scale is determined by the interaction between active particles, of both populations among themselves, and, for each of them, with particles of the lower system.

Technical calculations of the mathematical kinetic theory of active particles (see Chapter 2–4 of [11]) analogous to those used to derive Eq. (2) yield

$$\begin{cases}\partial_t\varphi(t,v) = R[\varphi,\varphi](t,v) + S[\varphi,\psi](t,v),\\ \partial_t f_i(t,u) = J[\mathbf{f},\mathbf{f}](t,u) + Q[\mathbf{f},\varphi](t,u)\quad i=1,2,\end{cases}\tag{6}$$

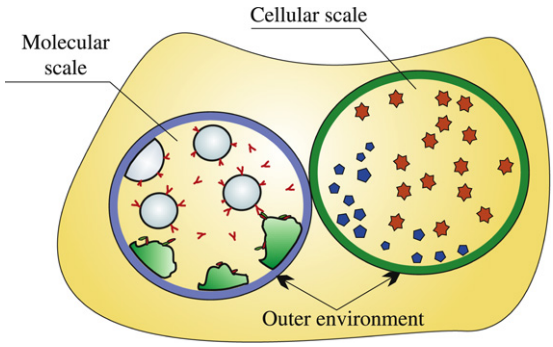

Fig. 1. Coupling of lower and higher scales under the action of the outer environment.

where the right hand side models the flow, at time t, into the elementary volumes $[v, v + \mathrm{d}v]$ and $[u, u + \mathrm{d}u]$ of the state space of the gene expression, and it is defined by the terms

$$R[\varphi, \varphi] = \int_{D_v \times D_v} \eta(v_*, v^*)\mathcal{B}(v_*, v^*; v)\varphi(t, v_*)\varphi(t, v^*)\,\mathrm{d}v_*\,\mathrm{d}v^* - \varphi(t, v)\int_{D_v} \eta(v, v^*)[1 - \mu_e(v, v^*)]\varphi(t, v^*)\,\mathrm{d}v^*, \tag{7}$$

and

$$S[\varphi, \psi] = \varepsilon_1 \int_{D_v \times D_v} \eta(v_*, v^*)\mathcal{C}(v_*, v^*; v)\varphi(t, v_*)\psi(t, v^*)\,\mathrm{d}v_*\,\mathrm{d}v^* - \varepsilon_1\,\varphi(t, v)\int_{D_v} \eta(v, v^*)[1 - \mu_s(v, v^*)]\psi(t, v^*)\,\mathrm{d}v^*, \tag{8}$$

while J_i has been defined in Eq. (2). Moreover

$$Q_i[\mathbf{f}, \varphi] = \varepsilon_2 \int_{D_u \times D_v} \eta(u_*, v^*)\mathcal{D}(u_*, v^*; u)f_i(t, u_*)\varphi(t, v^*)\,\mathrm{d}u_*\,\mathrm{d}v^* - \varepsilon_2 f_i(t, u)\int_{D_v} \eta(u, v^*)[1 - \mu_z(u, v^*)]\varphi(t, v^*)\,\mathrm{d}v^*. \tag{9}$$

where:

- η defines the rate of encounters between a *candidate* (or *test*) and a *field* particle in the molecular population related to conservative interactions.
- ε_1 and ε_2 define the scaling with respect to the rate of encounters between a *candidate* (or *test*) and a *field* particle in the molecular and cellular populations, respectively.
- $\mathcal{B}$, $\mathcal{C}$ and $\mathcal{D}$ define the probability densities, in the molecular and cellular populations, respectively, that a *candidate* particle modifies its state due to an encounter with a *field* particle of the molecular population and the outer environment. These terms have the structure of a probability density with respect to the output state:

$$\int_{D_v} \mathcal{B}(v_*, v^*; v)\,\mathrm{d}v = \int_{D_v} \mathcal{C}(v_*, v^*; v)\,\mathrm{d}v = \int_{D_v} \mathcal{D}(u_*, v^*; u)\,\mathrm{d}u = 1, \tag{10}$$

  for all input states.
- μ_e and μ_s define the net proliferation of a *candidate* particle, belonging to the molecular population, due to an encounter with a *field* particle of the molecular population or the outer environment respectively.
- μ_z defines the net proliferation of a *candidate* particle, belonging to the cellular population, due to an encounter with a *field* particle of the outer environment population.

Substituting all terms into (6) yields

$$
\begin{cases}
\partial_t \varphi(t,v) = \displaystyle\int_{D_v\times D_v} \eta(v_*,v^*)\mathcal{B}(v_*,v^*;v)\varphi(t,v_*)\varphi(t,v^*)\,\mathrm{d}v_*\,\mathrm{d}v^* \\
\quad -\varphi(t,v)\displaystyle\int_{D_v} \eta(v,v^*)[1-\mu_e(v,v^*)]\varphi(t,v^*)\,\mathrm{d}v^* \\
\quad +\varepsilon_1\displaystyle\int_{D_v\times D_v} \eta(v_*,v^*)\mathcal{C}(v_*,v^*;v)\varphi(t,v_*)\psi(t,v^*)\,\mathrm{d}v_*\,\mathrm{d}v^* \\
\quad -\varepsilon_1\,\varphi(t,v)\displaystyle\int_{D_v} \eta(v,v^*)[1-\mu_s(v,v^*)]\psi(t,v^*)\,\mathrm{d}v^*, \\
\partial_t f_i(t,u) = \displaystyle\sum_{j=1}^{2}\int_{D_u\times D_u} \eta_{ij}(u_*,u^*)\mathcal{A}_{ij}(u_*,u^*;u)f_i(t,u_*)f_j(t,u^*)\,\mathrm{d}u_*\,\mathrm{d}u^* \\
\quad -f_i(t,u)\displaystyle\sum_{j=1}^{2}\int_{D_u} \eta_{ij}(u,u^*)[1-\mu_{ij}(u,u^*)]f_j(t,u^*)\,\mathrm{d}u^* \\
\quad +\displaystyle\sum_{h=1}^{2}\sum_{k=1}^{2}\int_{D_u}\int_{D_u} \eta_{hk}(u_*,u^*)\mu_{hk}(i)(u_*,u^*;u)f_h(t,u_*)f_k(t,u^*)\,\mathrm{d}u_*\,\mathrm{d}u^* \\
\quad +\varepsilon_2\displaystyle\int_{D_u\times D_v} \eta(u_*,v^*)\mathcal{D}(u_*,v^*;u)f_i(t,u_*)\varphi(t,v^*)\,\mathrm{d}u_*\,\mathrm{d}v^* \\
\quad -\varepsilon_2 f_i(t,u)\displaystyle\int_{D_v} \eta(u,v^*)[1-\mu_z(u,v^*)]\varphi(t,v^*)\,\mathrm{d}v^*,
\end{cases}
\tag{11}
$$

with $i = 1, 2$. Some applications will be discussed in the next section.

4. Critical analysis

The contents of this present work have been proposed with methodological aims of looking at applications in various fields of life sciences such as those dealt with in the book [11], where interactions at different scales occur. For instance, this is the case for social sciences [12,13], where individual behaviours have an influence over the dynamics of groups of interest, and vehicular traffic [14], due to the influence of the heterogeneous behaviours of drivers. Of course, dealing with specific applications may need technical developments of the above approach as will be documented in a forthcoming paper, following this short note. In fact, the specificity of the interactions and that of the concept of scaling both depend on the particular system under consideration.

Finally, let us briefly consider the coupling with the higher scale. It has been shown in [15] that macroscopic equations can be derived from the underlying description delivered by the kinetic theory. The derivation is obtained by application of asymptotic methods after suitable time–space scaling. It has been shown how different equations correspond to different stages of the evolution, namely mass conservation, parabolic, and hyperbolic with onset of source terms [16–18]. Therefore, the evolution of the structure of macroscopic equations can be obtained by linking them to the equations at the lower scale, namely equations of the type (6). The reference background is the multiscale modelling of cancer phenomena where, as documented in [4], all scales are involved in the evolution of the system.

The coupling can be technically applied also in the case of scales different from those treated in the preceding sections. For instance, the approach proposed in [9] deals with the coupling between the cellular scale and the super-macroscopic scale. In this case, the parameters at the higher scale depend on the dynamics at the lower scale. This is a particular case that can be useful in several applications.

References

[1] L. Arlotti, N. Bellomo, E. De Angelis, Generalized kinetic (Boltzmann) models: Mathematical structures and applications, Math. Models Methods Appl. Sci. 12 (2002) 567–591.
[2] A. Bellouquid, M. Delitala, Modelling Complex Biological Systems—A Kinetic Theory Approach, Birkhäuser, Boston, 2006.
[3] N. Bellomo, G. Forni, Complex multicellular systems and immune competition: New paradigms looking for a mathematical theory, Curr. Top. Dev. Biol. 81 (2008) 485–502.
[4] N. Bellomo, N.K. Li, P.K. Maini, On the foundations of cancer modelling: Selected topics, speculations and perspectives, Math. Models Methods Appl. Sci. 18 (2008) 593–646.
[5] B. Vogelstein, K.W. Kinzler, Cancer genes and the pathways they control, Nat. Med. 10 (2004) 789–799.
[6] N. Komarova, Stochastic modeling of loss- and gain-of-function mutation in cancer, Math. Models Methods Appl. Sci. 17 (2007) 1647–1674.
[7] J. Tiuryn, D. Wójtowicz, R. Rudnicky, A discrete model of small paralog families, Math. Models Methods Appl. Sci. 17 (2007) 933–956.
[8] R.A. Weinberg, The Biology of Cancer, Garland Sciences - Taylor and Francis, New York, 2007.
[9] C. Cattani, A. Ciancio, Hybrid two scales mathematical tools for active particles modeling complex systems with learning hiding dynamics, Math. Models Methods Appl. Sci. 17 (2007) 171–188.
[10] N. Bellomo, M. Delitala, From the mathematical kinetic, and stochastic game theory to modelling mutations, onset, progression and immune competition of cancer cells, Life Sci. Rev. 5 (2008) 183–206.
[11] N. Bellomo, Modelling Complex Living Systems — A Kinetic Theory and Stochastic Game Approach, Birkhäuser, Boston, 2008.

[12] M.G. Bertotti, M. Delitala, Conservation laws and asymptotic behavior of a model of social dynamics, Nonlinear Anal. RWA 9 (2008) 183–196.
[13] N. Bellomo, M.G. Bertotti, M. Delitala, From the kinetic theory of active particles to the modelling of social behaviors and politics, Quality and Quantity 41 (2007) 545–555.
[14] M. Delitala, A. Tosin, Mathematical modelling of vehicular traffic: A discrete kinetic theory approach, Math. Models Methods Appl. Sci. 17 (2007) 901–932.
[15] N. Bellomo, A. Bellouquid, J. Nieto, J.J. Soler, Multicellular growing systems: Hyperbolic limits towards macroscopic description, Math. Models Methods Appl. Sci. 17 (2007) 1675–1693.
[16] N. Bellomo, A. Bellouquid, On the onset of nonlinearity for diffusion models of binary mixtures of biological materials by asymptotic analysis, Int. J. Nonlinear Mech. 41 (2007) 281–293.
[17] F.A. Chalub, Y. Dolak-Struss, P. Markowich, D. Oeltz, C. Schmeiser, A. Soref, Model hierarchies for cell aggregation by chemotaxis, Math. Models Methods Appl. Sci. 16 (2006) 1173–1198.
[18] P. Degond, S. Motsch, Continuum limit of self-driven particles with orientation interaction, Math. Models Methods Appl. Sci. 18 (2008) 1193–1217.